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Identification of Increased Blood Brain Barrier Permeability in the Substantia Nigra of the HIV-1 Transgenic Rat

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Neurologic symptoms were identified in HIV infected patients at the beginning of the AIDS epidemic. It eventually became clear that a subset of these symptoms could be attribute to HIV alone. The neurological symptoms were characterized as a subcortical dementia. For example, disorders of ocular motor mobility, gait abnormalities, postural problems, bradykinesia, slowed psychomotor response, depression, and bradyphrenia. These symptoms are also characteristic of Parkinson's disease. It was eventual confirmed that abnormalities to the dopaminergic system were present [1]. In addition, it was shown that Tat and Gp120 affected dopamine (DA) production [2]. DA receptor binding was also altered by HIV proteins. In HIV infection there can be a reduction of DA in the nigrostriatal dopaminergic pathway. The magnitude of the symptoms brought about by this DA deficiency was also correlated with Substantia Nigra (SN) neuronal loss [3]. Loss of tyrosine hydroxylase is another neural protein that was found to correlate with impairment of neurotransmission [4]. Neuropathology of brains from patients with marked disability reveal degeneration of SN neurons [5]. Currently, with very effective antiviral treatment, many of the central nervous system (CNS) problems were minimized or elimination. But HIV is not entirely eliminated from the CNS due to the microglial cells that can serve as viral reservoirs even with treatment. As a result, Parkinson like symptoms have the potential to occur over time. This creates a unique challenge to treatment. In order to address the pathologies that are found in the HIV/AIDS we developed the HIV-1 transgenic rat [6]. This model has been shown to produce GP-120, TAT and Nef. Our first report noted the symptomology related to Basal Ganglia dysfunction [6]. Subsequently, further studies provided clarification to changes of the dopaminergic system [7]. Further we note this rat model possesses a CXCR4 receptor capable of binding to GP-120. Therefor it is possible that the GP-120 can bind to CXCR4 positive cells associated with the DA system. In addition, it had been found that GP-120 can produce pathology in endothelial cells [8]. In the present investigation we looked at Blood Brain Barrier (BBB) leakage associated with the DA system. **Methods:** Adult HIV-1 TGRs [N=6] were perfused with buffered formalin. Coronal serial sections were produced including areas of the Caudate Putamen, and SN. Alternate sections were immunehisto-chemically labeled for Rat IgG, (a marker for BBB permeability) and Nissl Stain. In addition, Senescence Associated Beta-Gal enzyme (SABG) histochemistry was performed on 3 brains using frozen sections. Brain locations were determined by comparing them the rat stereotaxic atlas. (Fig 1 and 2) Several of these animals showed motor problems. **Results:** Two HIV-1 TGRs showed marked signs BBB permeability in the caudate/putamen as well as the SN (Fig 3 and 4). The intensity of labeling varied among animals from intense to not detected. Controls were negative. **Conclusion:** Noninfectious HIV comorbidities are an increasing health care challenge. This is particularly true of those morbidities that affect the brain. There are multiple factors that are contributing to the production of the

neuropathology associated with HIV infection. One mechanism is BBB alterations. The present model permits analysis of potential pathologic mechanisms and offers the possibility of testing neuro-protectants.

Nissl stain used to locate the SB.

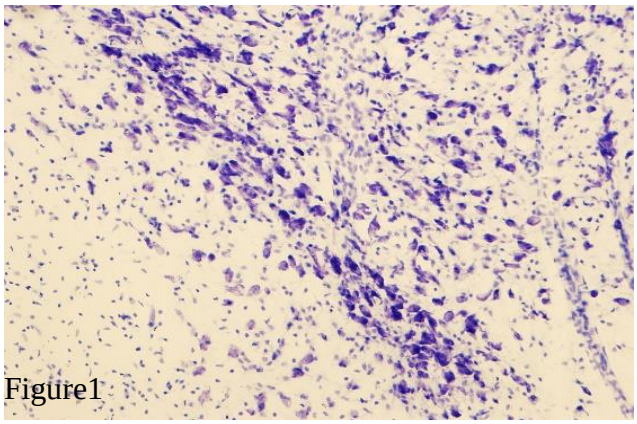

Figure 1 Nissl Stain, 10X of SN

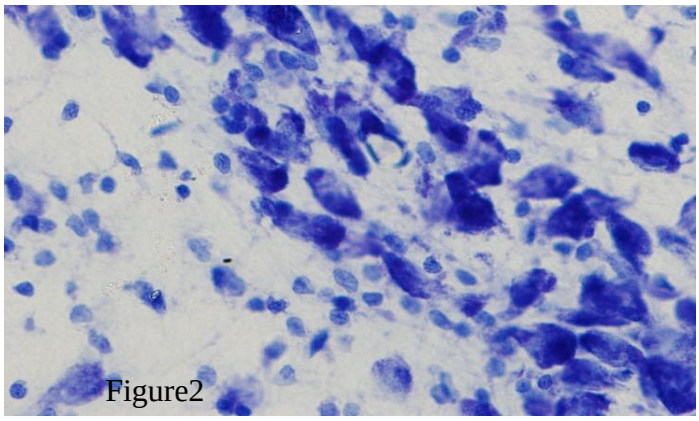

Figure 2 Nissl Stain, 20x SN

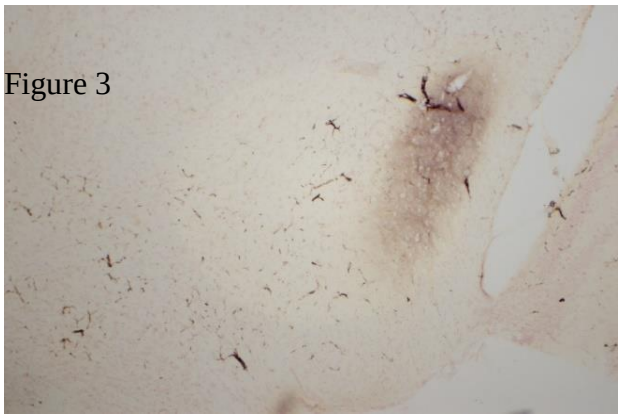

Figure 3 IgG immunocytochemistry, 10X of SN

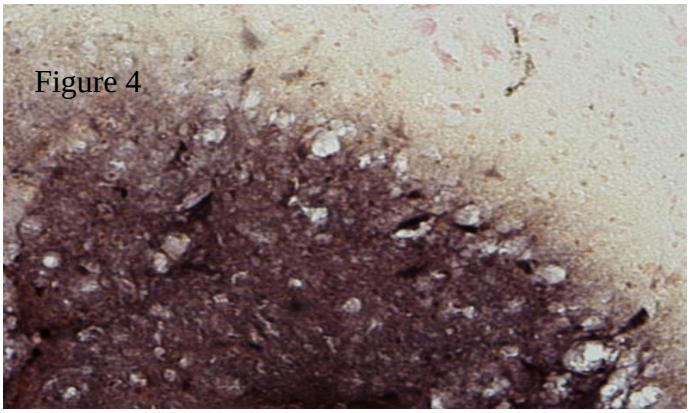

Figure 4 Nissl Stain, 40x Sn IgG immune cyto-Chemistry

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